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Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

PETITION FOR STAY OF ACTION

On behalf of Mutual Pharmaceutical Co., Inc. ("Mutual"), the undersigned submits this petition under 21 C.F.R. § 10.35 to request that the Commissioner of Food and Drugs ("FDA" or the "Agency") stay approval of any supplemental new drug application ("sNDA") for Skelaxin® (metaxalone) Tablets, including but not limited to NDA 13-217/S-046, until the Agency has fully evaluated and ruled upon the Citizen Petition recently filed by King Pharmaceuticals Inc. ("King"), Docket No. 2004P-0140/CP-1 (March 18, 2004), as well as all comments submitted in response to that petition, and any related cross-petitions that may be filed by any interested party. More specifically, and to effectuate the requested Stay, this Petition requests that FDA:

(a) Rescind, and/or stay the effect of, the March 12, 2004 "approvable" letter to King for NDA 13-217/S-046;

(b) Stay any approval of new Skelaxin labeling that recommends, requires, or otherwise discusses dosing the drug with food, either generally or for any subset of patients;

(c) Stay approval of *any* Skelaxin labeling changes until FDA:

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(i) has published the full text of the pending requested Skelaxin labeling changes, the clinical data submitted by King in support of the requested changes, and all clinical data and correspondence between Elan or King, and FDA, regarding proposed changes in the Skelaxin labeling since 2000; and

(ii) has accepted and considered comments from interested persons, submitted within 60 days of the publication of the information described in subparagraph (i) above, with respect to the validity and relevance of King's requested changes to the Skelaxin labeling, and any changes that may be necessary to allow generic applicants to carve out any protected information and allow immediate final approval of metaxalone ANDAs.

DECISION INVOLVED

The decision that is the subject of this Petition for Stay of Action is the possible final approval of new labeling for Skelaxin including, but not limited to, changes proposed under pending sNDA 13-217/S-046. That sNDA seeks to revise the pharmacokinetics section of the Skelaxin labeling, and to "recommend that Skelaxin be administered with food to ensure more consistent plasma levels of metaxalone." King Cit. Pet. at 8. That sNDA was deemed "approvable" in a letter from FDA dated March 12, 2004, and King has stated that it will respond with additional changes "shortly." If FDA hastily approves the sNDA without the benefit of fully considering the important medical, legal, and public policy issues implicated by King's Citizen Petition and comments to that Petition currently being prepared by Mutual, Mutual and American consumers could be inappropriately denied the benefits of lower cost generic metaxalone products for many years to come. This irreparable harm far outweighs any harm (of which there is actually none) to King if the Stay is granted.

ACTION REQUESTED

Mutual requests that FDA stay any final approval of NDA 13-217/S-046, or any other labeling supplement, for Skelaxin® (metaxalone) Tablets until FDA has fully evaluated and ruled upon King's Citizen Petition, comments filed in response thereto, and any related cross-petitions that may be filed by an interested party. The actions requested in this Stay Petition are necessary to assure that FDA does not inadvertently facilitate an anticompetitive scheme by King to prevent generic competition for metaxalone tablet drug products using faulty medical assumptions derived from dubious scientific data.

STATEMENT OF GROUNDS

The Requested Stay Is In The Public Interest, In The Interest Of Justice, And Is Supported By Sound Public Policy Grounds. Moreover, Mutual Will Be Irreparably Harmed Absent A Stay, And A Stay Is Not Outweighed By Any Other Public Interests

The Commissioner may grant a Stay Petition if it is in the public interest and in the interest of justice. 21 C.F.R. § 10.35(e). Moreover, FDA must grant a stay in any proceeding if: The petitioner will otherwise suffer irreparable injury; the petitioner's case is not frivolous and is being pursued in good faith; the petitioner has demonstrated sound public policy grounds supporting the stay; and the delay resulting from the stay is not outweighed by public health or other public interests. *Id.* The criteria for both a discretionary stay and a mandatory stay are met in this case, and the requested stay should therefore be granted.

Skelaxin has been marketed under a New Drug Application (NDA), and/or pursuant to a DESI determination of safety and efficacy, since before 1962, but to the detriment of American consumers there has never been a generic version of Skelaxin. The stay requested herein is necessary to assure that this lack of consumer choice and price competition for metaxalone does not continue for yet a third generation of Americans as a result of the anti-competitive tactics being employed by King.

For the past 40+ years, Skelaxin's labeling has not included any specific instructions vis a vis dosing with or without food, but it was recently discovered that metaxalone bioavailability differs depending on whether the drug is dosed under fed or fasting conditions. However, to this day, there is no clinically significant evidence to suggest that the safety or effectiveness of Skelaxin is altered based on whether the drug is dosed in a fasting or fed condition. *See* King Cit. Pet. at Ex. 6, p. 3, n. 3 (noting that no study has been submitted by King "to demonstrate a clinical effect arising from the difference in fed- and non-fed-state bioavailability."). Nevertheless, for the past several years King and Elan Pharmaceuticals Inc. (the previous owner of the Skelaxin NDA) have been pursuing a strategy to leverage dubious patents and a handful of small, clinically inconclusive bioavailability studies into an additional long-term barrier to generic competition. Unfortunately for American consumers, the King/Elan scheme has already delayed the availability of lower cost generic metaxalone products for several years, and if the requested stay is not granted, FDA approval of King's proposed labeling

changes may inappropriately solidify King's stranglehold on the metaxalone market without conferring any medical or economic benefits on American consumers.

This Petition does not challenge King's right to make Skelaxin labeling changes, where such changes are legally permissible, not anti-competitive, and reflect clinically important and relevant information. However, King's sNDA does not appear to meet any of these criteria. Rather, King's sNDA clearly falls into the category of "Generic Defense" or "Lifecycle Management" strategies that branded drug companies have increasingly been adopting to delay – for as long as possible, and by any means – generic threats to even the longest running drug monopolies.

As FDA is well aware, one of the more problematic anti-generic tactics involves NDA sponsors seeking minor but patented or exclusivity-protected labeling changes that make it difficult or impossible for generic applicants to exercise their rights under 21 U.S.C. § 355(j)(2)(A)(viii) and 21 C.F.R. § 314.04(a)(12)(iii) to obtain approval of competing products that "carve out" the protected aspects of labeling. FDA has recognized and proposed solutions to the potential anti-competitive outcomes of such marginal labeling changes, including changes that relate to dosing instructions. FDA explained the problem in a Draft Guidance as follows:

> When the holder of the innovator drug obtains approval and market protection for a change to the drug and removes the corresponding unprotected information from the current labeling, there is no current complete labeling for the ANDA applicant to reference. For example, the NDA holder may obtain approval and market protection for a new dosing regimen and remove the previous dosing regimen(s) from the labeling. In this situation, the ANDA applicant, which must include information regarding dosing regimen in its

> application, is blocked by the NDA holder's exclusivity from referencing the new dosing regimen contained in the innovator drug labeling, and all the previous dosing regimen information has been removed from the current labeling. This raises the question of whether applicants will be barred from obtaining approval for any ANDA for that innovator drug until the protection for the new dosing regimen expires, because relevant labeling is either protected or has been removed from the currently marketed product.[3]
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> [3] In theory, the innovator could delay generic competition indefinitely by continuing to make minor — but protectable — changes to the drug, and removing unprotected labeling. If this approach were effective, the Agency also could expect to review many more labeling supplements, possibly for changes that, although sufficiently innovative to warrant patent or exclusivity protection, do not necessarily represent significant improvements in the currently marketed drug.

Draft Guidance for Industry: *Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications*, at 2 (Oct. 2000). King is clearly following a form of the discontinued labeling strategy that FDA identified in the Discontinued Labeling Guidance – pursuing Skelaxin labeling "changes that, although sufficiently innovative to warrant patent or exclusivity protection, do not necessarily represent significant improvements in the currently marketed drug." Because FDA has not yet finalized the regulatory solution proposed in the Guidance, it is even more important that FDA grant the requested stay so that future Skelaxin labeling changes (if any) do not impede prompt approval of safe, effective, and more affordable generic metaxalone products.[1]

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[1] One recent example of such tactics involved the drug Ultram (tramadol) where the NDA sponsor added a new, marginally useful dosing regimen applicable only to the treatment of chronic pain patients not requiring rapid pain relief. The dosing for acute pain patients remained the same as when Ultram was originally approved, but because FDA allowed the NDA sponsor to alter other non-exclusive aspects of the Ultram labeling in such a way as to make it grammatically difficult to "carve out" the newly exclusive dosing regimen, the entry of generic tramadol

(Footnote continued)

Mutual's requested stay is further supported by the fact that King itself has chosen to make the issue of the clinical relevance of the Skelaxin labeling a matter of public debate and decisionmaking by FDA through the Citizen Petition process. By filing a Citizen Petition asking FDA to determine that food effect labeling is clinically relevant and necessary for the safe use of metaxalone tablet products, King has directly opened for public debate the clinical relevance of the four small pharmacokinetic studies, and the "meta-analysis" of those studies, which King submitted in support of the proposed labeling changes that are the subject of this Stay Petition. However, King has failed to disclose the data and reports from the studies cited in its Citizen Petition, Studies 101, 103, 105, and 106, even though the Petition directly relies upon those studies and reports in support of the relief requested by King. *See* King Cit. Pet. at 5-8.

Moreover, King apparently numbered its metaxalone studies in single digit sequence (evidenced by citation to studies 105 and 106) yet the Petition makes no reference to Study 102 or Study 104. These studies presumably exist, but the glaring absence of any reference or explanation of their findings in King's Petition strongly suggests that the results are unfavorable to King's Petition, and to King's requested labeling changes as well.[2] Only by staying approval of any Skelaxin labeling changes

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was significantly delayed, to the detriment of American consumers. *See* FDA Dockets Nos. 02P-0191 and 01P-0495.

[2] The absence of actual study data and reports from *all* metaxalone bioavailability studies conducted by King also calls into question the accuracy of King's signed certification that its "petition includes all information and views on which the Petition relies, and that it includes representative data known to the Petitioner which are unfavorable to the Petition."

until the data and reports that form the underpinnings of King's petition are made public for scrutiny and comment can FDA assure that critical mistakes are avoided in the approval of any additional Skelaxin labeling supplements.

The stay requested in this Petition is in the public interest, is in the interest of justice, and is supported by sound public policy grounds, because it will provide time, and a necessary and appropriate mechanism, for FDA to work with all interested parties to assure that only well-supported labeling changes are approved for Skelaxin and that such changes (if any) are implemented in such a way as to not deprive generic applicants of their equally important rights to market their products with labeling that omits patent-protected labeling. In this way, the requested stay would protect the American public's right to the earliest possible access to lower cost generic metaxalone products, as intended by Congress under the Hatch-Waxman Amendments. Therefore the requested stay may, and should, be granted pursuant to 21 C.F.R. § 10.35.

Not only does FDA have the discretion to grant the stay, as shown above, under the circumstances here FDA is obligated to grant the stay: "The Commissioner shall grant a stay in any proceeding if all of the following apply: (1) The petitioner will otherwise suffer irreparable injury; (2) The Petitioner's case is not frivolous and is being pursued in good faith; (3) The petitioner has demonstrated sound public policy grounds supporting the stay; (4) The delay resulting from the stay is not outweighed by public health or other public interests." 21 C.F.R. § 10.35(e).

If a stay is not granted, Mutual will suffer irreparable injury. Mutual has invested substantial time and resources in developing a lower priced generic alternative to Skelaxin, and overcoming the various hurdles King and Elan have already put in its way. These hurdles have included meeting the new requirement that generic metaxalone products demonstrate bioequivalence by *in vivo* studies in patients in both fasting and fed states. This difficult bioequivalence standard, which was prompted by an Elan Citizen Petition, imposed several additional years of delay as Mutual worked to comply with FDA's new requirement, notwithstanding that FDA has correctly determined that the food effect suggested by the Elan/King pK studies has no known clinical relevance, and more specifically that "there are no data to support an increase in adverse events related to increased drug concentrations." *See* King Cit. Pet. Ex. 6 at 4 (FDA Letter to Metaxalone ANDA Applicants, March 1, 2004).

A second and related hurdle put before generic applicants by King and Elan is the listing in the Orange Book of the '128 Patent (and more recently the '102 Patent), each of which King claims covers a method of increasing the bioavailability of metaxalone by administering the drug with food. *See* Orange Book Use Code U-189 ("enhancement of the bioavailability of the drug substance."). Because of this patent listing, generic applicants were required to include in their ANDA *either* a patent certification, or a method of use ("section (viii)") statement notifying FDA that the ANDA does not seek approval of any use claimed by Patent '128. FDA initially refused to allow Mutual to file a section (viii) statement, but Mutual, working with FDA over the course of nearly a year,

successfully established that a method of use statement is appropriate given the lack of clinical relevance of food effect information in the Skelaxin labeling. Now, after overcoming all these hurdles, Mutual faces the prospect that a rushed FDA decision to approve King's pending labeling supplement will inadvertently nullify Mutual's costly, pro-competitive investments. The harm to Mutual without a stay is thus significant and irreparable.

Finally, any delay caused by granting the stay will not be outweighed by any other public health or public interest considerations. King is still free to market Skelaxin using existing labeling and would thus suffer no economic disadvantage by a stay. Moreover, the proposed changes to Skelaxin's labeling are not clinically significant and are not necessary for the continued safe and effective use of Skelaxin. As FDA determined *after* having reviewed King's most recent food effect data for nearly a year, "omission of information regarding fed-state bioavailability will not negatively affect the safe use of metaxalone." King Cit. Pet. Exs. 5, 6.[3] Thus, Skelaxin users will not be at risk during the requested stay, and there is no other public health interest that outweighs the benefits of granting a stay.

CONCLUSION

As demonstrated herein, the Stay requested by this Petition is in the public interest and in the interest of justice. This alone is sufficient grounds for FDA to grant the stay.

[3] As King's own exhibits show, King submitted its age- and gender-related food effect data and meta analysis to FDA on April 21, 2003. FDA concluded that food effect data is not clinically significant on March 1, 2004, and issued an "approvable" letter to King based on the April 2003 data, on March 12, 2004.

Moreover, this Petition is being pursued in good faith and is not frivolous, and Mutual has shown sound public policy grounds in support of the stay. And, if FDA were to refuse the stay and precipitously approve a Skelaxin labeling supplement that does not allow for a generic labeling "carve out," Mutual and American consumers would suffer irreparable injury by reason of the further delay in generic competition for metaxalone tablet products. For those reasons, FDA *may* and *must* grant the Petition and stay approval of King's sNDA 13-217/S-046 (and any other Skelaxin labeling supplement) until the Agency has fully evaluated and ruled upon the King Citizen Petition, all comments submitted in response thereto, and any related cross-petitions that may be filed by any interested party.

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